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Please find below and/or attached an Office communication concerning this application or proceeding.

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/619,539
Filing Date: July 16, 2003
Appellant(s): BOSCH ET AL.

Michele M. Simkin
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 02/05/10 appealing from the Office action mailed 09/08/09.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

Claims 1-3, 5-35, 37, 39, 41, 43-52, 54-82 and 84-123 are pending in the application.

Claims 46-52, 54-82 and 84-123 are withdrawn.

Claims 1-3, 5-35, 37, 39, 41 and 43-45 are rejected.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office

action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

5302401	Liversidge et al.	04-1994
WO0178505A1	Brockbank et al.	10-2001
20030077329	Kipp et al.	04-2003
20050004049	Liversidge	01-2005

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 2 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The present specification discloses that only certain nanoparticulate active agents from needle-like crystals in a liquid dosage composition (page 21, lines 1-2). The specification further disclosed that the active agent of the present invention is of a type that forms undesirable crystals during storage and/or heat sterilization (page 21, lines 5-7). The specification, however, does not show if all of the active agents disclosed in pages 21-23 possess the claimed limitation, which form undesirable crystals during storage and/or heat sterilization. Absent a clear indication from the present specification, a burdensome amount of research would be required by one of ordinary skill in the art determine the storage condition of the unlimited number of active agents disclosed in the present specification.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 15 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 15 is being rejected for failing to further limit the subject matter of claim 1. While claim 15 requires that the composition is a tablet, a fast melt, or a lyophilized formulation, claim 1 recites that the composition is a liquid dosage form.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 5, 6, 8-19, 21-24, 27-29, 32-35, 37, 39, 41 and 43-45 are rejected under 35 U.S.C. 102(b) as being anticipated by Liversidge et al. US 5,302,401 (Liversidge '401).

Liversidge '401 teaches a suspension composition comprising of nanoparticles having a surface modifier adsorbed on the surface thereof, and a cryoprotectant associated with (abstract). Surface modifier includes the claimed surface stabilizer. See column 2. Combination of two or more surface modifier is taught in column 2, lines 65-68. The amount of surface modifier ranges from about 0.1% to about 90% by weight based on the total combined weight of the drug substance add the surface modifier (column 3, lines 31-35). Cryoprotectant includes mannitol and glycerol (column 5, lines 27-30). Cryoprotectant is used in an amount of 0.5% to 90% based on the total weight of the nanoparticulate suspension (column 5, lines 37-39). Liversidge '401 further teaches the viscosity of the suspension is less than about 1000 centipoise (column 3,

lines 36-38). The average particle size of the nanoparticle is less than 400 nm (column 5, lines 1-14). The active agent has particle size of less than about 400 nm (column 5, lines 45-48). Liversidge '401 further teaches that liquid medium such as water can be used as the pharmaceutically acceptable carrier (column 5, lines 53-55).

It is of note that Liversidge '401 does not explicitly teach the claimed properties such as: the amount of active agent per ml is equal to or greater than the amount of the active agent per ml of a standard conventional non-nanoparticulate liquid dosage composition of the same active agent; and the pharmacokinetic, e.g., T_{max} and C_{max} of the composition.

However, such properties are inherent because Liversidge '401 teaches the same nanoparticulate composition comprising the same surface stabilizer and cryoprotectant (osmotically active crystal growth inhibitor) in the claimed amounts, which exhibits the property desired by applicant, namely, a nanoparticulate composition that is stable and have reduced or no particle size growth (column 1, lines 28-34). This is also because when the claimed and prior art products are identical or substantially identical in structure or composition, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977).

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-3, 5-24, 26-31, 35, 37, 39, 41 and 43-45 are rejected under 35 U.S.C. 102(e) as being anticipated by Kipp et al. US 2003/0077329.

Kipp discloses a stable suspension of poorly water soluble pharmaceutical agent. The suspension comprises nanoparticles of a pharmaceutical active agent having average diameter less than about 200 nm suspended in an aqueous matrix, and one or more excipients (abstract; and paragraphs 0042, 0050, 0078 and 0084). Excipients include: 1) two or more surface modifiers (paragraphs 0063-0068); 2) crystal growth modifier (paragraph 0070); 3) cryoprotectant compounds (paragraph 0071); and osmotic agent such as mannitol, glycerol, and sodium chloride (paragraph 0073). Excipients are used in an amount ranges from 0.001-20% (paragraph 0075). The suspension is suitable for a wide variety of administration including parenteral (abstract; and paragraph 0043).

It is noted that Kipp does not explicitly teach the claimed properties such as: the amount of active agent per ml is equal to or greater than the amount of the active agent per ml of a standard conventional non-nanoparticulate liquid dosage composition of the same active agent; and the pharmacokinetic, e.g., T_{max} and C_{max} of the composition.

However, such properties are inherent because Kipp teaches the same nanoparticulate composition comprising the same surface stabilizer and osmotic agent in the claimed amounts, which exhibits the property desired by applicant, namely, a stable nanoparticulate composition suitable for poorly water soluble active agent (paragraph 0004). This is also because when the claimed and prior art products are identical or substantially identical in structure or composition, a prima facie case of

either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977).

Claim Rejections - 35 USC § 103

Claims 1-3, 5-24, 27-29, 32-35, 37, 39, 41 and 43-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liversidge '041, in view of Brockbank et al. WO 01/78505 A1 or Kipp et al. US 2003/0077329.

Liversidge is relied upon for the reason stated above. Liversidge does not explicitly teach cryoprotectant compound includes sodium chloride, and in the case that applicant selects other crystal growth inhibitor from the Markush group recites in claim 1. Brockbank teaches cryoprotectant compound includes lactose, mannitol, mannose, glycose, xylitol, sorbitol, magnesium chloride, propylene glycol, glycerol, or sodium chloride (paragraph 0024).

Kipp discloses a stable suspension of poorly water soluble pharmaceutical agent. The suspension comprises nanoparticles of a pharmaceutical active agent having average diameter less than about 200 nm suspended in an aqueous matrix, and one or more excipients (abstract; and paragraphs 0042, 0050, 0078 and 0084). Excipients include: 1) two or more surface modifiers (paragraphs 0063-0068); 2) crystal growth modifier (paragraph 0070); 3) cryoprotectant compounds (paragraph 0071); and osmotic agent such as mannitol, glycerol, and sodium chloride (paragraph 0073). Excipients are used in an amount ranges from 0.001-20% (paragraph 0075).

Thus, it would have been obvious to one of ordinary skill in the art to, by routine experimentation optimize the nanoparticle composition of Liversidge '401 to include sodium chloride in view of the teachings of Brockbank or Kipp. This is because Brockbank teaches that lactose, mannitol, mannose, glycose, xylitol, sorbitol, magnesium chloride, propylene glycol, glycerol, and sodium chloride are well known cryoprotectant compounds, because Kipp teaches a stable nanoparticulate composition with the use of the claimed osmotic agent such as mannitol, glycerol, or sodium chloride, and because Liversidge '401 teaches the desirability for using agents such as mannitol, glycerol, and the like.

Claims 25-35, 37, 39, 41 and 43-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liversidge '401, in view of Liversidge US 2005/0004049 (Liversidge '049).

Liversidge '401 is relied upon for the reason stated above. The reference does not teach the claimed specific active agent suitable in a bioadhesive composition.

Liversidge '049 teaches a nanoparticulate composition comprising surface modifier, and a drug having solubility of less than about 30 mg/ml (abstract; and paragraph 0045). Drug including analgesic, NSAID and vitamins are discloses in paragraphs 0109-0113). The nanoparticulate composition is processed into a liquid dosage for bioadhesive composition (paragraphs 0081-0089). Liversidge further teaches the claimed viscosity, C_{max}, T_{max}, and bioequivalency (paragraphs 0090-0105). Thus, it would have been obvious to one of ordinary skill in the art to modify the

nanoparticulate composition of Liversidge ‘401 to include active agents in view of the teachings of Liversidge ‘049 to obtain a useful bioadhesive composition of the present invention. This is because Liversidge ‘049 teaches that the claimed active agents in nanoparticulate dosage form are known in the art, and because Liversidge ‘401 teaches a stable nanoparticulate composition suitable for a wide variety of active agents.

(10) Response to Argument

With respect to the 112 rejections of record, Appellants indicate that appropriate claim amendment, if necessary, be made by way of an Examiner’s Amendment upon receipt of a favorable decision on the appeal from the Board. Therefore, the 112 rejections are maintained.

Appellants argue that Liversidge '401 is irrelevant to obtaining a stable nanoparticulate active agent liquid dosage composition. Rather, Liversidge '401 targets the problem of particle size growth during a lyophilization process. See column 1, lines 17-34. In other words, unlike the claimed liquid dosage composition, the nanoparticulate active agent composition of Liversidge '401 is in lyophilized dry powder form.
More specifically, Liversidge '401 discloses contacting a nanoparticulate active agent composition with a cryoprotectant, which functions to prevent active agent particle size growth during lyophilization, and then allowing the composition to be lyophilized. See column 1, lines 36-49, and 56-58. Although cryoprotectants of Liversidge '401 encompass some pharmaceutical ingredients overlapping the osmotically active crystal growth inhibitors of the claimed invention, one skilled in the art would not have obtained

the claimed liquid dosage based on the prior art's disclosure of a lyophilized composition. Accordingly, Appellants respectfully request the Board to reverse the rejection over Liversidge '401.

However, in response to Appellants' argument that *unlike the claimed liquid dosage composition, the nanoparticulate active agent composition of Liversidge '401 is in lyophilized dry powder form*, the Examiner notes that the therapeutic or diagnostic nanoparticles are admixed in a solution of cryoprotectant (column 5, lines 63-67). From this excerpt, it can be seen that a liquid formulation is obtained that comprises nanoparticles of therapeutic or diagnostic suspended in a solution of cryoprotectant. Therefore, Liversidge '401 does teach a liquid dosage form as claimed. Moreover, in response to Appellants' arguments with respect to the lyophilization step, it is noted that the rejected claims do not preclude the liquid formulation to be lyophilized solely for storage purpose. Appellants' attention is also called to the teachings in Example 1, where Liversidge teaches that the freeze dried powder can then be reconstituted to give a liquid formulation.

Appellants argue that the claimed invention relates to a stable nanoparticulate active agent liquid dosage composition. Kipp discloses prolonging the storage of a suspension of drug particles "by encasing the drug particles in a frozen aqueous matrix" because drug dissolution and degradation will be slowed down at low temperature and crystallization of water may help to prevent crystal growth of drug particles. Page 4, paragraph [0039]. Accordingly, Kipp does not teach or suggest stabilizing a

nanoparticulate active agent liquid dosage composition by adding an osmotically active crystal growth inhibitor. Rather, Kipp solves the problem by storing the composition at freezing temperature so that the drug particles are "encased in a frozen aqueous matrix." As such, Kipp does not teach a liquid dosage to anticipate the claimed invention. Reversal of the rejection in whole is respectfully requested.

However, in response to Appellants' arguments with respect to Kipp, the Examiner notes that the present claims do not preclude storing the liquid composition in the frozen state to *prolong* the storage stability of the composition. Kipp teaches that lower temperatures slow down the spontaneous degradation of the drug molecules in the aqueous medium to improve their chemical stability (paragraphs 0039 and 0054), and improve stability for a prolonged period of time (abstract; and paragraph 0047). From these teachings, it can be seen that the "frozen" step is an added benefit to further improve the storage stability.

Appellants argue that Brockbank and Kipp are cited for the alleged teaching of additional cryoprotectant compounds. Office Action, page 7, second full paragraph; and the paragraph bridging pages 7 and 8. First, Liversidge '401 is directed to a lyophilized dry powder composition rather than a liquid dosage composition as in the claimed invention. Therefore, the alleged teachings of additional cryoprotectant compounds by the secondary references would not have cured the deficiencies of Liversidge '401. Second, as discussed above, Liversidge '401 attempts to obtain a stable nanoparticulate active agent composition by lyophilizing the composition to prolong the

storage in dry powder form. Although Kipp shares the common goal of obtaining a stable composition, Kipp achieves the goal by encasing the composition in a frozen aqueous matrix at low temperature. Accordingly, one skilled in the art would not have had any reason to combine the teachings of Liversidge '401 and Kipp because these references take entirely different approaches that would have rendered the proposed modification impossible. Pursuant to M.P.E.P. 2143.01, "[i]f the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious."

However, in response to applicant's arguments, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). Brockbank and Kipp are cited solely for the teaching of cryoprotectant that includes sodium chloride.

Appellants argue that Liversidge '049 is cited for the alleged teaching of a bioadhesive nanoparticulate active agent composition. Nevertheless, Liversidge '049 does not compensate for the deficiencies of Liversidge '401. Therefore, the rejected dependent claims will stand or fall together with the base claim(s).

However, in response to applicant's argument *that Liversidge '049 does not compensate for the deficiencies of Liversidge '401*, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). Liversidge '049 is cited solely for the teaching of the use of bioadhesive nanoparticulate active composition.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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